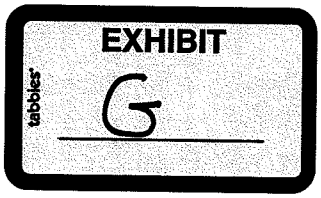

LEXSEE 208 USPQ 343

UNITED STATES PATENTS QUARTERLY

Ex parte Engelhardt

No Number in Original

U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences

208 U.S.P.Q. (BNA) 343

Opinion dated Apr. 23, 1980

CASE HISTORY and DISPOSITION: Appeal from Group 125.

Application for reissue of patent of Edward L. Engelhardt, Serial No. 776,464, filed Mar. 10, 1977 for reissue of Patent No. 3,428,735 issued Feb. 18, 1969. From decision rejecting claims 1, 2, and 3, applicant appeals (Appeal No. 424-40). Affirmed.

HEADNOTES:
PATENTS

[1H]** 1. Specification -- Sufficiency of disclosure (62.7)

Evidence subsequent to filing date cannot be used to show what inventor contemplated to be his best mode at time application was filed.

PATENTS

[2H]** 2. Applications for patent -- Continuing (15.3)

Statute provides that later filed application cannot obtain benefit of filing date of parent application if parent does not comply with requirements of first paragraph of *35 U.S.C. 112.*

[3H]** 3. Patentability -- Tests of -- Skill of art (51.707)

One skilled in art area pertinent to antidepressant drugs would be familiar with principles of both organic and medicinal chemistry.

[4H]** 4. Patentability -- Invention -- In general (51.501)

Absolute predictability is not required by patent statutes; *35 U.S.C. 103* merely requires that there be reasonable expectation, or some predictability.

[5H]** 5. Patentability -- Composition of matter (51.30)

Patentability -- Evidence of -- Solution by several parties (51.465)

Patentability -- Invention -- In general (51.501)

Simultaneous discovery of drug's activity is convincing evidence of obviousness of this property and clearly indicates that art available to those working in this area suggested this activity; prima facie showing of obviousness may be overcome by showing of unexpected properties or advantages.

Particular patents -- Amitriptyline

Engelhardt, Method of Treating Depression With 5-(3-Dimethylaminopropylidene) Dibenzo (a,d) (1,4)Cycloheptadiene Or Its Non-Toxic Salts Thereof, rejection of claims 1, 2, and 3 affirmed on new grounds.

CLASS-NO: 15.3, 51.30, 51.465, 51.501, 51.707, 62.7

COUNSEL: Carroll G. Harper, Nels T. Lippert, and Fitzpatrick, Cella, Harper & Scinto, all of New York, N.Y., and Rudolph J. Anderson, Rahway, N.J., for appellant.
Donald R. Dunner, Robert D. Bajefsky, and Finnegan, Henderson, Farabow, Garrett & Dunner, all of Washington, D.C., for protestor.

JUDGES: Before Magil and Merker, Examiners-in-Chief, and Rzucidlo, Acting Examiner-in-Chief.

OPINIONBY: Rzucidlo, Acting Examiner-in-Chief.

OPINION:
This is an appeal from the final rejection of claims 1, 2 and 3 which are the only claims presented in the instant application. In addition, we have before us a request by protestor Biocraft (hereinafter "protester") to enter a new ground of rejection under the provisions of 37 CFR 1.196(b).

Claims 1, 2 and 3 read as follows:

1. A method of treating human mental disorders involving depression which comprises orally administering to a human affected by depression 5-(3-dimethylaminopropylidene) dibenzo(a,d) (1,4)cycloheptadiene or its non-toxic salts in daily dosage of 25 to 250 mg. of said compound.

2. The method of claim 1 in which said cycloheptadiene is the hydrochloride salt.

3. The method of claim 1 in which said cycloheptadiene is the hydrobromide salt.

Brief History of Application and Issues Before Board The instant application for reissue has been filed by appellant under the provision of 37 CFR 1.175(a)(4) in order to cite prior art not previously considered by the examiner. The specification and claims of the instant application are identical with those of appellant's Patent No. 3,428,735 (hereinafter the Engelhardt patent). The Engelhardt patent issued from an application filed on August 24, 1967 which was a continuation-in-part of an application filed on November 30, 1959. This patent is the subject of litigation styled as Biocraft Laboratories, Inc. v. Merck & Co., Inc., Civil Action No. 77-0693, which is now pending in the United States District Court of **[*344]** New Jersey. Since Biocraft has been accused by Merck of infringement of the Engelhardt patent, Biocraft has actively participated in the prosecution of the reissue application as provided for in 37 CFR 1.291. The issues before us on appeal are the propriety of rejections of the instant claims by the examiner under the first paragraph of *35 USC 112, 35 USC 102* and *35 USC 103.* In effect, the examiner has adopted protestor's section 112 position asserting that the instant application and its parent applications fail to disclose the best mode contemplated by the inventor. As for the rejections under sections 102 and 103 of the Statute, the examiner, as well as protestor, assert that the instant application, which because of its reissue status is in effect a reexamination of the 1967 application, should not be accorded the benefit of the filing date of the 1959 application and conclude that a number of references which have publication dates prior to the 1967 filing date may be applied against the instant claims. In addition, protestor has requested that the Board enter new rejections under the provisions of 37 CFR 1.196(b) based upon *35 USC 112,* first paragraph and *35 USC 103.* The issues have been thoroughly briefed and argued by appellant, protestor and the examiner. Numerous documents have been presented as evidentiary support for the respective positions of appellant and protestor. We have carefully considered all of the arguments and evidence presented in the instant record in rendering our decision.

The references relied upon by the examiner are:

Freed, American Journal of Psychiatry, Vol. 117, pages 455 and 456, Nov. 1960.

Ayd, Psychosomatics, Vol. 1, No. 6, pages 320 through 324, 1960.

Barsa, American Journal of Psychiatry, Vol. 117, pages 739 and 740, Feb. 1961.

Hucker, Abstract 46,584 of article appearing in Federation Proceedings, Vol. 20, page 20, March, 1961.

Dunlop, Dis. Nerv. System, Vol. 22, pages 107, 108 and 109, April, 1961.

Alexander, Dis. Nerv. System, Vol. 22, pages 14 through 23, May, 1961.

Feldman, Dis. Nerv. System, Vol. 27, pages 27 through 30, May, 1961.

Lauter, Abstract 55,933 of article appearing in Munchen Med. Wehnschr., Vol. 104, pages 2236 through 2246, Nov. 1962.

British Medical Journal, Vol. 1, pages 173 and 174, Jan. 1963, Abstract no. 59504. Hordern, British Journal of Psychiatry, Vol. 109, pages 815 through 825, Nov. 1963.

Browne, British Journal of Psychiatry, Vol. 115, pages 693 through 696, 1969.

The references cited by the Board are:

Mills	3,189,657	June 15, 1965 (Eff. Nov. 3, 1960)
Rey-Bellet et al (Rey-Bellet)	3,384,663	May 21, 1968 (Eff. March 27, 1959)
Villani	3,409,640	Nov. 5, 1968 (Eff. July 22, 1959)

Friedman, First Symposium On Chemical-Biological Correlation, pages 296 through 358, May 26-27, 1950.

Burger, Journal of Chem. Ed., Vol. 33, pages 362 through 372, 1956.

Kuhn, Schweizerische Medizinische Wochenschrift, Vol. 87 (35/36), pages 1135 through 1140, 1957.

Geigy Research Report No. 43,162 pages 1 through 9, Nov. 1957.

Geigy Research Report No. 43,169, pages 1 through 8, April 16, 1958.

Geigy Research Report No. 52,195, pages 1 through 13 September 19, 1958.

Petersen et al. (Petersen), Arzneimittel-forschung, Vol. 8, No. 7, pages 395, 396 and 397 (1958). n1

n1 Original not in record. We have relied upon translation attached as exhibit V of protest against reissue, paper No. 6.

Lehmann et al (Lehmann) Canadian Psychiatric Association Journal, Vol. 3, No. 4, pages 155 through 164, Oct. 1958.

Van Meter et al. (Van Meter) ibid., Vol. 4, pages 5113-5119, 1959.

Hafliger, ibid., Vol. 4, pages 569-574, 1959.

Villani et al. (Villani), Journal of Medicinal and Pharmaceutical Chemistry, Vol. 5, pages 373 through 383, 1962.

Winthrop et al., Journal of Org. Chem., Vol. 27, pages 1230 through 1240 (1962).

Best Mode Rejection Claims 1, 2 and 3 have been finally rejected under *35 USC 112,* first paragraph as failing to set forth the best mode contemplated by the inventor to carry out the instant invention.

We cannot sustain the examiner's rejection.

In order to make clear the reasons for our decision, we will discuss the chronology of events that took place during the prosecution of appellant's 1959 and 1967 applications, as well as the instant application. **[*345]**

The disclosure in appellant's 1959 application taught the antidepressant activity of 5-(3-dimethylamino-propylidene) dibenzo(a,d) (1,4) cycloheptadiene (hereinafter "amitriptyline") and it indicated that this compound may be administered in a daily dose of from 25 to 250 milligrams, preferably in divided doses throughout the day. The 1967 application from which the Engelhardt patent issued and the instant application both recite this same dosage range. There are no other teachings relating to dosages in any of these applications. Hence, these disclosures would indicate that the best mode contemplated by appellant at the time of filing of each of these applications was the administration of from 25 to 250 mg of amitriptyline in divided dosages throughout the day. Affidavits have been submitted signed by Dr. Engelhardt, the inventor, and Dr. Bayne, the assistant medical director at Merck in 1959, in which affiants aver that a dosage range from 25 to 250 mg/day was the best mode contemplated by the inventor and by others at Merck as of the filing date of the 1959 application. Appellant asserts that there has not been any evidence presented to support a finding that this range was not the best mode contemplated by the inventor.

The examiner and protester assert that there is no evidence presented to show that, prior to November 30, 1959, Dr. Engelhardt or anyone else at Merck considered 25 mg/day to be an effective antidepressant dosage for amitriptylene. Documents of record establish that Merck initially advised physicians testing amitriptylene that 12.5 mg to 25 mg three times per day would probably be a good starting dosage. After initial test results had been obtained, Merck began to advise clinicians to administer amitriptylene in amounts of 25 to 75 mg three times a day. Most physicians used dosages of between 75 mg and 300 mg per day. However, there is some evidence that at least one physician used as little as a 37.5 mg per day starting dosage which was quickly increased to 75 mg or more per day. There is no evidence presented to show that, prior to the filing date of the 1959 application, anyone was advised to use 25 mg of amitriptylene per day or that such a dosage was considered to be effective.

In preparing the 1959 application for filing, Merck's patent attorney requested information as to the effective dosage of the instant compound and was told that the preferred daily dose is from 75 to 250 mg. Neither the inventor nor the patent attorney can recall the circumstances under which the preferred dosage was changed to 25 to 250 mg per day in the patent application. Deposition testimony simply presents speculation as to what might have occurred or the possible reasoning for this broadened dosage range.

In summary, there are isolated instances of clinicians who used 50 mg per day or 62.5 mg per day and some indication that, at least initially, 37.5 mg per day was a suggested dosage. There is simply no evidence that, prior to November 30, 1959, 25 mg per day or any dosage between 25 mg and 37.5 mg per day was contemplated as being a useful dosage for amitriptylene. The evidence does show that 75 mg was considered to be the best starting dosage.

From the various dosage ranges that were possible appellant chose to insert into his 1959 application a range which the evidence does not show to have been contemplated as being useful. We conclude that the 1959 application does not disclose the most effective dosage range, i.e., the best mode, which the evidence before us supports. Through the use of a broad range which does include the narrower range actually contemplated as the useful effective dosage, appellant, in effect, concealed his true best mode. *Dale Electronics, Inc. v. R.C.L. Electronics, Inc., 488 F.2d 382, 180 USPQ 225* (1st Circuit, 1973); and *Indiana General Corp. v. Krystinel Corp., 421 F.2d 1023, 164 USPQ 321* (S.D. N.Y., 1968), aff'd *164 USPQ 321* (2d Cir, 1970).

Go to Headnotes **[**1R]** [1] While it may be true that dosages may vary according to the illness or patient involved, it is clear that at the time prior to the filing of the 1959 application, no one at Merck considered low dosages of between 25 to 37.5 mg per day to be effective for any condition or patient. Evidence subsequent to the filing date cannot now be used to show what the inventor contemplated to be his best mode at the time the application was filed. In short, the 1959 application disclosure does not differentiate the range that was known to be effective from the speculative range of from 25 to 250 mg per day. Hence we are of the opinion that the range recited in the 1959 application was not the best mode contemplated or known at that time.

The situation differs for the 1967 application from which the Engelhardt patent issued. Our consideration of the evidence leads us to conclude that there were sufficient data available at the time of the filing of the 1967 application that the inventor could have included 25 mg as the lower limit **[*346]** of the dosage range representing the best mode of the instant invention. Clinicians' reports giving the results of the use of amitriptylene in patients in amounts as little as 25 mg per day were received by Merck in early to mid-1960 and are summarized in a document listed as attachment B to paper No. 51 of the instant application. This document describing the early clinical work performed to evaluate the effectiveness of amitriptylene contains references to clinically administered doses of 25, 30, 37 1/2 , 40 and 50 mg per day and is dated November 22, 1960. Exhibit 12 attached to appellant's brief (paper No. 65) is a report by Dr. Bowers of the use of amitriptylene at a starting dose of 12.5 mg two times per day in a 67 year old female patient suffering from depression and anxiety. A significant improvement was noted in the patient after 14 days and the patient continued on this medication for 4 months. The effect of the medication on the patient's symptoms was less anxiety and depression. Dr. Bower in his letter to Merck indicates that amitriptylene might not be useful as a mood elevator, and notes that he thinks the greatest usefulness for this drug is in nondepressing tranquilization. However, it is clear from the report that even 25 mg per day does relieve depression to some extent. Even though several other clinicians reported the use of a 25 mg per day dosage, there is no indication of the effect of the medication at this level upon the patient.

In addition to these clinical reports, several publications appeared prior to the filing date of the 1967 application which reported the administration of amitriptylene at dosages of 25 mg daily or other dosages lower than 75 mg daily. These publications were listed in exhibit B of paper No. 26 of the instant application. For convenient reference we reproduce a few of these citations and summaries thereof as given in the exhibit.

Zelcer, "Amitriptyline: An Effective Treatment in Dermatology", El Dia Medico 33: 424-426, April 10, 1961 (Translation p. 4):

"In adults, fear, anxiety, restlessness, insomnia and tendency to weeping disappeared, and the mental state improved. In children, the drug suppressed agitation and tendency to weeping and crying and improved behavior.

"(4) The dosage used was 25-75 mg a day in adults and 12.5 to 37.5 mg in children up to 12 years old."*

H. Lauter, "Psychiatric Pharmacotherapy, Its Place in the Pattern of Treatment of Endogenous Psychoses", Munchen med. Wchnschr. 104: 2236-2246, Nov. 16, 1962 (Translation p. 27):

"Table 3

Psychodrug Maintenance Doses

Brand Name	Psychoph. Effect	Generic	Daily Maintenance dose in mg.
Laroxyl	T	Amitriptyline	25-100
Saroten	T	Amitriptyline	25-100
Tryptizol	T	Amitriptyline	25-100"**

Edward Dunlop, "The Treatment of Depression in Private Practice", March, 1961 -- Read at the Symposium on Depression, Eastern Psychiatric Research Association, Incorporated, Waldorf-Astoria Hotel, New York City, New York, March 4, 1961 (p. 7):

"* * * For office patients it is surprising how many excellent results can be produced with a very small dose as low as 10 mgm. t.i.d. This is most effective in the neurotic type depression who generally overact to phenothiazine tranquilizers and barbiturates and tend grossly to exaggerate the sedative effect of these compounds."

G. Fiegel, "Effect of a Situation of Psychic Stress on Chronic Heart Disease", Arztl. Praxis 13: 1990-1991, September 30, 1961 (Translation p. 5):

"As to dosage, 10-mg. and 25-mg. tablets are available. An initial dosage of three times 25 mg. seems suitable, and this may be reduced to smaller doses of two to three times 10 mg. after overcoming the vegetative dysregulation, but this is again dependent on the individual * * *"

Seymour Diamond, M.D., "Use of Amitriptyline Hydrochloride in General Practice", The Illinois Medical Journal, April, 1963 (pp. 347-348):

"The initial dosage was 25 mg. t.i.d. or q.i.d. for two to eight weeks. The dosage was then reduced to 10 mg. t.i.d. or b.i.d., depending upon the severity of the complaints. Some patients with mild depression or anxiety, as well as adolescent and elderly patients, were satisfactorily treated with 10 mg. q.i.d. * * *"

Marvin Hader, J.J. Madonick, "Experiences with Amitriptyline in Elderly **[*347]** Patients", American Journal of Psychiatrics, 122: 1289-1291, May, 1966 (p. 1291):

"It would seem that the use of amitriptyline in the elderly patient is practicable and essentially safe. In low doses (10-75 mgm. per day) it often effectuates remission of symptoms and permits adequate management without the necessity of other procedures. It can be given to the very elderly patient providing elementary precautions of dosage, recognition of target symptoms, and observation for the presence of side effects are part of the total procedure."

A. J. Krakowski, "Recent Advances In Psychopharmacology -- A Review", Medical Times, Vol. 94, No. 10: 1209-1217, October, 1966 (p. 1215):

"* * * With dosages of 10 to 40 mg/day initially and 20 to 75 mg/day for maintenance, satisfactory response with onset from 2 to 4 weeks, was observed in 68% of cases in the first study and 72% in the second, with the following order of improvement. * * *"

It appears that low dosages including 25 mg daily were not the most effective mode of administration. However, the evidence does show that some relief from depression or anxiety could be obtained at low dosages including 25 mg daily. Since all these data were available to appellant prior to the filing of the 1967 application, we are of the opinion that appellant could reasonably have considered a range of between 25 and 250 mg per day to be within the best mode of practicing his invention.

Rejection Over Intervening References Claims 1, 2 and 3 have been finally rejected under *35 USC 102* or in the alternative under *35 USC 103* over any one of the following: Freed, Abstract of the British Med. Journal article, Dunlop, Hucker or Lauter.

All the cited references disclose the use of amitriptylene as an antidepressant and are, in fact, directed to the same subject matter as recited in the instant claims. They have publication dates subsequent to the filing date of the 1959 application, but prior to the filing date of the 1967 application from which the Engelhardt patent is issued. It is the examiner's position that since the 1959 application does not comply with the requirements of *35 USC 112,* first paragraph, the instant application should not be accorded the benefit of the November 30, 1959 filing date. We affirm the examiner's rejection.

The instant application is an application for reissue filed under the provisions of 37 CFR 1.175(a)(4). All of the claims and the disclosure of the instant application are identical to the claims and disclosure of the original patent. In effect, examination of the instant application constitutes a reexamination of the 1967 application. Because of this, *35 USC 252* specifically provides that the claims of the reissue application shall "have effect continuously from the date of the original patent." Section 1401.09 of the M.P.E.P. clearly recites as follows:

"To be effective, a reference must be prior to the effective filing date of the original patent."

Go to Headnotes **[**2R]** [2] Appellant's 1967 application is a continuation-in-part of the 1959 application and, in fact, contains the same disclosure as the earlier filed application. The only change in the 1967 application is the addition of claims to the method of using amitriptylene as a depressant specifically in humans. In order to avoid the references cited by the examiner, in the instant rejection, appellant would have to obtain the benefit of the filing date of the 1959 application as provided for in *35 USC 120.* The Statute provides that a later filed application cannot obtain the benefit of the filing date of the parent application if the parent does not comply with the requirements of the first paragraph of *35 USC 112.*

In view of our finding, discussed hereinabove, that the 1959 application did not comply with the best mode requirement, appellant's 1967 application cannot be accorded the benefit of the filing of its parent application. Hence, the intervening references are available as prior art against the instant claims and render the instant invention unpatentable.

Request for New Rejections Under 37 CFR 1.196(b) Protestor has requested that the Board make new rejections of the appealed claims under the provision of 37 CFR 1.196(b). As basis for these rejections, protestor asserts that the instant claims are based upon a non-enabling disclosure *(35 USC 112,* first paragraph) and that the instant claims would have been obvious under *35 USC 103.* We have carefully considered appellant's and protestor's arguments and we conclude that the subject matter of the claims on appeal would have been obvious **[*348]** within the meaning of *35 USC 103.* However, we do not agree that there is any basis for entering a new rejection under *35 USC 112,* first paragraph.

Refusal to Enter New Rejection for Lack of Enablement As noted by appellant, the situation in the instant application substantially differs from the facts of *In re Gardner, 57 CCPA 1207, 427 F.2d 786, 166 USPQ 138* which is relied upon by protestor. The instant record contains a significant amount of evidence relating to the nature of depression and its treatment. Appellant does not urge any use for amitriptylene except for the treatment of depression in humans. Those skilled in the art to which the instant disclosure is directed would clearly understand from appellant's specification that the most likely host for treatment of depression is man rather than animal. In spite of the intention of the patent attorney who drafted the instant application, the skilled artisan would realize that animals are not customarily treated with antidepressants to relieve depression. This is basically a human malady. The dosage range disclosed by appellant is 25 to 250 mg per day as compared with 10 to 450 mg per day in Gardner. Evidence of record indicates this to be a reasonable range of dosage in relation to the plasma levels of amitriptylene found in patients. This dosage range is well within the dosages used for similar drugs such as imipramine or chloropromazine which are prescribed for depressed patients. We agree with appellant and the examiner that the instant disclosure when viewed in conjunction with the evidence of record does comply with the enabling requirement of *35 USC 112.*

New Rejection Under *35 USC 103* Claims 1, 2 and 3 are rejected as being unpatentable under *35 USC 103.* As evidence of obviousness, we refer to the references indicated as being cited by the Board and listed at the beginning of this opinion.

The instant invention is directed to a method of treating depression in humans by administering an organic compound known as amitriptylene in a particular dosage range. Amitriptylene is not the first material used in the treatment of depression and, in fact, is closely related in structure to the known antidepressant imipramine. The issue before us in considering the instant claims on their merits for patentability is whether the artisan having the requisite skill in the pertinent art area and a knowledge of the available prior art would have been motivated to employ amitriptylene in the treatment of human depression.

In *Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966)* it is stated that the question of obviousness under *35 USC 103* is to be determined as follows (pp. 17-18, *148 USPQ 466-467*):

"Under 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness, these inquiries may have relevancy."

Our discussion in setting forth the instant invention will follow the stepwise analysis set forth in Graham v. Deere.

Scope and Content of Prior Art Depression, the illness which is treated in the instant invention, is one of the most frequently occurring and clinically heterogeneous psychiatric disorders. Depressive diseases are not only dangerous and widespread but also involve much suffering for not only the patient but also the patient's family. Early modes of treatment of depression included electroshock, opium extract, and monoamine oxidase inhibitors. Electroshock therapy, although disagreeable to both patient and doctor, is still used for severely depressed patients. Opium cure was not found to be particularly effective and the side effects of monoamine oxidase inhibitors have limited their usefulness.

In 1957 Kuhn (cited hereinabove) reported that a drug named imipramine having the following structural formula: (Source Materials are available by calling BNA PLUS, (800) 452-7773 nationwide, or (202) 452-4132 in Washington, D.C.)

was tested on a number of patients having endogenous depressions and was found to have an antidepressant action. Imipramine is a iminodibenzyl derivative whose develop **[*349]** ment stemmed from interest in a structurally related group of compounds known generally as phenothiazines which have the following structural formula: (Source Materials are available by calling BNA PLUS, (800) 452-7773 nationwide, or (202) 452-4132 in Washington, D.C.)

Two of the more important drugs which were of therapeutic value in the treatment of psychiatric disorders that are phenothiazine derivatives are promazine and chlorpromazine and have the structures indicated below. (Source Materials are available by calling BNA PLUS, (800) 452-7773 nationwide, or (202) 452-4132 in Washington, D.C.) (Source Materials are available by calling BNA PLUS, (800) 452-7773 nationwide, or (202) 452-4132 in Washington, D.C.)

Like the phenothiazine compounds, imipramine proved to be active in the potentiation of narcosis and "artificial hibernation". See Hafliger. In fact, Kuhn reported that imipramine manifested a therapeutic effect comparable to that of chlorpromazine although in a somewhat less potent and predictable manner. Van Meter investigated the mechanisms of action of imipramine and chlorpromazine and found some differences as well as some similarities. Lehmann also noted the structural similarities between imipramine and the phenothiazine derivatives and reported that imipramine depresses or inhibits most of the perceptual, psychomotor and cognitive functions tested and, compared to the phenothiazines, imipramine seems to exert more pronounced effects on the cerebral cortex. In summary, the prior art recognized a structural similarity between imipramine and phenothiazines as well as some similar modes of action but also found that these compounds differ in that the phenothiazines function as sedatives while imipramine is an active antidepressant.

At about the same time as the activity of imipramine was being investigated, Petersen reported the synthesis of another class of compounds which were structurally related to the phenothiazines and studied the pharmacological effectiveness of these materials. Thiaxanthenes, as this series of compounds was called, had a structure wherein the nitrogen of the phenothiazine was replaced with an unsaturated carbon atom. It was reasoned that, since the pi-electron distribution in the phenothiazine derivatives and the thiaxanthene compounds must be the same, there should be no loss in pharmacodynamic activity between these classes of compounds. This conclusion was confirmed by experimental data. Specifically, chlorpromazine (structure shown above) and chlorprothixene (structure shown below) showed essentially the same biological activity even though the nitrogen of the phenothiazine had been replaced by an unsaturated carbon. (Source Materials are available by calling BNA PLUS, (800) 452-7773 nationwide, or (202) 452-4132 in Washington, D.C.)

The prior art useful against the instant claims includes the compound amitriptylene itself, the compound but not its antidepressant activity being prior art by virtue of the adverse decision against appellant in Interference No. 92, 336. Amitriptylene has the following structural formula: (Source Materials are available by calling BNA PLUS, (800) 452-7773 nationwide, or (202) 452-4132 in Washington, D.C.)

Skill and Knowledge of the Artisan Go to Headnotes **[**3R]** [3] Since the instant invention is directed to a method of treating depression in humans by administering an organic compound having a particular chemical structure, one skilled in the art area pertinent to the instant invention would be familiar with the principles of both organic and medicinal chemistry. Drugs useful in the treatment of mental disorders are developed by the systematic molecular modification of known materials. Such structural variations may increase the therapeutic usefulness of a known drug by widening the differences between desirable actions and toxic reactions. New groups can be introduced into the molecules of the active compound or removed by chemical degradation to produce materials having altered biological properties.

If functional groups capable of withdrawing or repelling electrons are located in the chain or ring of a biologically active compound, transfer of such groups to other positions in which their electronic effects are lessened or enhanced may alter the biological activity of the modified compound. Hence, position isomerism has been used as a tool to obtain new and useful **[*350]** drugs. The concepts of optical, geometrical and conformational isomerism and the effect of such changes in known active materials have also been employed by chemists as avenues to obtain novel drugs.

The physical properties of biologically useful substances have been determined and compared with biological activity. It has been found that these properties play an important role in the absorption, pharmacological transport mechanism, adsorption and excretion of drugs. In order for a drug to act in a host organism, the drug must be adsorbed onto a complementary receptor surface in the host. This adsorption mechanism requires that the drug have a certain size, shape, stereochemistry, electronic distribution and distribution of functional groups within the drug molecule. The discovery of a new and useful drug usually gives rise to an extended search for closely related compounds having a similar size, shape, stereochemistry and electronic configuration in order to obtain a drug which has a similar, more effective, more specific or even opposite activity.

Isosterism involves the substitution in a parent compound of one atom or a group of atoms for another atom or group of atoms having a similar electronic and steric configuration. This concept, although not generally discussed in organic chemistry texts, is a familiar concept in medicinal chemistry books. The articles by Burger and Friedman which have been cited by us contain extensive discussions of the principles of isosterism as applied to the field of medicinal chemistry. Originally, isosterism was applied to explain the similarities in the physical properties of simple molecules but was later expanded to larger molecules whose peripheral electronic structures are identical. Various pairs of atomic groupings because of their electronic structure are considered to be equivalent. Thus =CH is equivalent to =N-, and -S- is equivalent to the resonating -CH=CH-. A comparison of aromatic systems such as benzene and thiophene, or pyridine and thiazole shows a striking similarity of many important physical properties. (Source Materials are available by calling BNA PLUS, (800) 452-7773 nationwide, or (202) 452-4132 in Washington, D.C.) (Source Materials are available by calling BNA PLUS, (800) 452-7773 nationwide, or (202) 452-4132 in Washington, D.C.) (Source Materials are available by calling BNA PLUS, (800) 452-7773 nationwide, or (202) 452-4132 in Washington, D.C.) (Source Materials are available by calling BNA PLUS, (800) 452-7773 nationwide, or (202) 452-4132 in Washington, D.C.)

Burger points out that isosteric replacement causes considerable overlap in the effect of organic compounds on the same enzyme system. These ideas have been applied in the field of antihistaminic and antispasmodic drugs having the general formula: (Source Materials are available by calling BNA PLUS, (800) 452-7773 nationwide, or (202) 452-4132 in Washington, D.C.)

where A and B may be cyclic systems such as benzene, thiophene, furan, thiazole or pyridine; Y is =CH- or -N-, or -O-; and Z is an aliphatic or simple cyclic tertiary amino group, often -N(CH[3])[2] . Similarity of molecular size and shape is the guide used in recognizing potential similar or antagonistic biological action in related structures.

Isosterism is the theoretical basis for the work done by Petersen wherein the nitrogen of the phenothiazine nucleus was replaced by an unsaturated carbon atom. Similarly, Hafliger, Van Meter and Lehmann recognized the isosteric relationship between promazine and imipramine, i.e., the replacement of the sulfur atom of the phenothiazine with a -CH[2] - CH[2] - group. Although the isostere of a known biologically active compound may have an antagonistic effect as compared to the known drug, there is no reason to doubt the validity or usefulness of the theory of bio-isosterism. As Friedman notes "In either case, it is proof that isosteric replacement gives compounds acting by the same mechanism, that they are truly bio-isosteric." Because of this, isosterism is one of the methods frequently used by medicinal chemists in their search for better physiologically active compounds.

Difference Between Instant Invention and Prior Art The instant method differs from the prior art in the use of amitriptylene rather than imipramine in the treatment of depression. Amitriptylene is structurally different from the known antidepressant in that the nitrogen of imipramine has been replaced by an unsaturated carbon atom. Although there are differences in the biological activity of these compounds, both are used almost exclusively in the treatment of depression.

Conclusion of Obviousness The issue before us is whether or not one skilled in the pertinent art area would have expected the replacement of the nitrogen atom in the known antidepressant with an unsaturated carbon to produce a com-

pound which would be useful in the treatment of **[*351]** depression. Our consideration of all of the evidence in the instant record leads us to conclude that the difference between the instant invention and the prior art would have been obvious within the meaning of *35 USC 103.* It is our opinion that the skilled medicinal chemist having the benefit of the Hafliger, Van Meter and Lehmann disclosures as well as a thorough knowledge of the investigative techniques used in this art area, including the concept of isosterism, would have concluded that amitriptylene would be an antidepressant. In fact, the evidence before us indicates that four other groups of inventors independently discovered amitriptylene's antidepressant properties using reasoning which was exactly the same as used by appellant.

In the reissue oath, appellant states that his knowledge that the isosterically related compounds known as chlorpromazine and chlorprothixene possessed the same biolgical activity coupled with Kuhn's discovery that imipramine was useful as an antidepressant led him to conclude that amitriptylene would also be useful for this purpose. This same line of reasoning was used by Villani, Mills, Rey-Bellet and Winthrop in their discoveries of this utility for amitriptylene.

Specifically, the Geigy Research Reports recognize the structural relationship between amitriptylene and imipramine and conclude that amitriptylene should be tested for antidepressant activity. The Geigy Reports are actually dated prior to the filing date of the 1959 application. Villani filed a patent application prior to the filing date of the Englehardt 1959 application which disclosed amitriptylene and its use in treating depression. In a later published journal article, Villani discusses the subject matter disclosed in the patent application and indicates that the principles of isosterism led to the discovery of this biological property. Similarly, Winthrop recognized the isosteric relationship between the new compound and the known drug, imipramine, and proceeded to prepare amitriptylene and test it for antidepressant activity. Although the date of the Winthrop journal article is subsequent to the initial reports of amitriptylene's activity, deposition testimony by Dr. Winthrop indicates that he had no knowledge of these reports. Finally, Mills in a patent having an effective filing date of November 3, 1960 reports the discovery of amitriptylene and its usefulness in the treatment of various depressive states. There is no indication of how Mills made this discovery. However, it remains a fact that Mills made the same discovery as appellant at approximately the same time and in light of the same prior art and skill in the pertinent art.

Appellant asserts that isosterism is not a well known concept and provides little or no guidance about the potential properties of a new compound. We cannot subscribe to this position. It is evident from the deposition testimony of various employees of Merck that isosterism was a known and recognized concept in medicinal chemistry. The fact that physicians or organic chemists were either unfamiliar or vaguely familiar with isosterism is not unexpected in that this concept is within the realm of medicinal chemistry. As noted hereinabove, the art area pertinent to the instant invention is medicinal chemistry. Hence, one of ordinary skill in medicinal chemistry would have looked to the concept of isosterism as a routine tool in his or her research. Furthermore, it appears that appellant as well as at least three other research teams used this concept in their research involving amitriptylene.

Go to Headnotes **[**4R]** [4] It is also argued that the concept of isosterism cannot be used to predict the properties of organic compounds with any degree of certainty. Although isosterism does not permit a medicinal chemist to predict the potential properties of a new isosterically related compound with absolute certainty, it does provide a suggestion of areas of biological activity. In any event, absolute predictability is not required by the Patent Statues. Section 103 of the Statute merely requires that there be a "reasonable expectation, or some predictability". *In re Kratz, 592 F.2d 1169, 201 USPQ 71* ; and *In re Kronig, 539 F.2d 1300, 190 USPQ 425* .

Go to Headnotes **[**5R]** [5] In summary, imipramine and amitriptyline are unquestionably closely related in structure. Both are tricyclic dibenzo compounds, one having a propyl amine side chain, the other a propylidene amine side chain. In a manner similar to other tricyclic dibenzo compounds having the same side chain, both imipramine and amitriptylene act on the central nervous system. It is in this area of closely related compounds that isosteric replacement has been most useful for medicinal chemists. Hence, Petersen found that the replacement of the nitrogen atom in the phenothiazine nucleus of chlorpromazine with an unsaturated carbon atom produced a compound having the same tranquilizing properties as the known material. Dr. Engelhardt, as well as four other groups of researchers, conceived of amitriptyline's an **[*352]** tidepressant properties almost as soon as the antidepressant activity of imipramine was reported by Kuhn. This simultaneous discovery of amitriptyline's antidepressant activity is convincing evidence of the obviousness of this property and clearly indicates that the art available to those working in this area suggested this activity. *Lerner et al. v. Child Guidance Products, Inc., 398 FSupp 1406, 193 USPQ 329* , *Sidewinder Marine, Inc. v. Starbrick Kustom Boats and Products, 193 USPQ 776* and *The Ceco Corp. v. Bliss & Laughlin Industries, Inc., 557 F.2d 687, 195 USPQ*

337 . The evidence in the instant record clearly establishes not only that one skilled in the art would have been motivated to use amitriptyline to treat depression, it also establishes that several workers were so motivated. We conclude that the appealed claims are prima facie obvious. Although a prima facie showing may be overcome by a showing of unexpected properties or advantages, the instant record does not contain sufficient evidence in this regard. *In re Lintner, 59 CCPA 1004, 458 F.2d 1013, 173 USPQ 560* . We also note that the instant application merely discloses that amitriptylene is useful as an antidepressant and does not teach any special or unusual properties for this compound.

New Rejection Under *35 USC 102* Claims 1, 2 and 3 are rejected under *35 USC 102* as being anticipated by Villani, Mills or Winthrop.

All of the cited references disclose the same invention as recited in the appealed claims and have effective filing dates prior to the earliest filing date accorded by us to the Engelhardt patent, i.e., August 24, 1967. An affidavit or declaration filed under the provisions of 37 CFR 1.131 containing averments as to conception, reduction to practice and diligence may be submitted in order to antedate any reference which does not constitute a statutory bar under *35 USC 102*(b).

Any request for reconsideration or modification of this decision by the Board of Appeals based upon the same record must be filed within thirty days from the date hereof (37 CFR 1.197).

With respect to the new rejection under 37 CFR 1.196(b), should appellant elect the alternate option under that rule to prosecute further before the Primary Examiner by way of amendment or showing of facts, or both, not previously of record, a shortened statutory period for making such response is hereby set to expire thirty days from the date of this decision. In the event appellant elects this alternate option, in order to preserve the right to seek review under *35 USC 141* or 145 with respect to the affirmed rejection, the effective date of the affirmance is deferred until conclusion of the prosecution before the examiner unless, as a mere incident to the limited prosecution, the affirmed rejection is overcome.

If prosecution before the examiner does not result in allowance of the application or a second appeal, this case should be returned to us for final action on the affirmed rejection, including any timely request for reconsideration thereof.

The decision of the examiner is affirmed.

Affirmed, new rejections 37 CFR 1.196(b)

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